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The Pathophysiological Role of Diet in Non-Communicable Disease Etiology

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Abstract

Background and aims*. Adherence to healthful diet has been a challenge both in the developing and developed countries due to the changes in lifestyles, access to ready junk food, resource constraints, lack of adequate knowledge, poor regulatory approaches and culture, to mention but a few, making the world population more vulnerable to non- communicable diseases (NCDs). By implication, an unhealthy diet is an important factor for disability and death relative to the increasing global NCD burden. This review updates knowledge on the role and dimension of diet and health outcomes such as; cardiovascular diseases, chronic obstructive pulmonary diseases, diabetes, and cancer.*

Methods*. A Systematic review of reviews and meta-analyses on chronic health outcomes attributable to dietary patterns were studied. In total, 141 reviews and meta-analyses were searched in Google Scholar, PubMed, Medline but 41 reviews published from 2016 onwards were included in the study.*

Results*. Consumption of a diet rich in animal fats, excessive energy, animal proteins, posed a higher risk or death due to NCDs. Alternatively, diets comprised of vegetables, fruits, nuts, low carbohydrates, low polyunsaturated fat, seafood, legumes, nuts, less meat, fish, and whole-grain were found to be protective for most NCDs.* ***Conclusions****. Research confirms diet to be both a risk factor (unhealthful diet) and at the same time protective (healthful diet) for NCDs. However, further epidemiological studies should emphasize the assessment of Health outcomes based on the quantity, frequency, concentration, synergistic interactions of various dietary nutrients.*

Keywords*: diet, non- communicable diseases, pathophysiology, role.*

Introduction

Non-communicable diseases (NCDs) are noninfectious health conditions typically caused by genetic and/or environmental and lifestyle factors. As NCDs tend to be long-lasting or recurrent, they are sometimes also referred to as chronic diseases. Currently, NCDs account for almost two-thirds of deaths and disabilities globally. Four main diseases account for the majority of deaths from NCDs: cardiovascular disease, chronic respiratory disease, cancer, and diabetes. Importantly, these four NCDs share common behavioral risk factors including tobacco use, unhealthy diet, physical inactivity, and harmful use of alcohol world Health Organization (WHO, 2016; Mwangi et al., 2018; U.S Global Non- Communicable Disease Efforts (UGNCDE), 2019). It is also stated that 80% of chronic disease deaths are already occurring in low- and middle-income countries (LMICs), yet in the past, NCDs have termed diseases of the rich in the developed countries (Akinwale, 2016). NCDs exacerbate and promote poverty while at the same time hindering economic development in low- and middle-income countries and should the upward trend remain unaverted, by 2030, chronic diseases will account for 70% of total global deaths and 56% of the global disease burden, coupled with an estimated cumulative production deficit of $47 trillion between 2011 and 2030 (Allen, 2017, UGNCDE, 2019). The epidemiological change will also place tremendous pressure on the health systems of nations, especially those in the least developed countries, as they must be confronted with a double burden of acute and chronic diseases amidst scarce resources (WHO, 2017; Gebremariam, 2018, Bertram et al., 2019).

The role of diet in the pathophysiology of non-communicable diseases (NCDs) has attracted debate among scientists for a greater part of history. In this context, diet refers to the negative impact of taking unhealthful foods that are high in carbohydrates, animal-based proteins and dietary fats as well as excessive salt and sugar intake, on the increased risk of NCDs, compared to having a healthful diet with adequate amounts

of vegetables, whole grain, fruits, olive oil, (Tan et al., 2017; Bingsilley et al., 2018; Phillips et al., 2019), low-fat or non-fat dairy, seafood, fish, legumes, and nuts; moderate in alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and drinks and refined grains is largely protective for such NCD conditions, commonly referred to as " Mediterranean Diet"(Hazavehei et al., 2018). Each person's dietary habit is likely to be influenced by various matters, including availability and affordability of food such as meat, fish, vegetables and fruits, lifestyle and work conditions, family habit, social pressure from friends and colleagues, cultural beliefs and traditional customs, personal preference, and lack of nutritional knowledge (Gebremariam et al., 2018).

Available information indicates that a total of 6.9 million male deaths (237.4 deaths per 100 000) and 5.2 million female deaths (147.0 deaths per 100 000) worldwide in 2015 were attributable to poor dietary habits. The population attributable fraction was 22.4% for males and 20.7% for females. Although the estimated mortality rate attributable to poor dietary factors decreased by 15.0% in the worldwide population from 2005 to 2015, the population attributable fraction increased by 7.9% over the same time period (Benjamin et al., 2018).

Nutrition is important in human health as it provides essential building blocks for growth, development, and maintenance of a healthy status throughout life. In this context, the co-existing burdens of undernutrition and overnutrition represent a paradigm shift for health authorities requiring appropriate dietary management recommendations. Modern lifestyles and easy access to high-energy, low-nutrient rich foods are considered part of the problem. For example, the economic costs of unhealthy diets and low physical activity in the EU were calculated to be €1.3billion per year. Currently, health authorities mainly target problems associated with obesity and cardiovascular diseases by focusing on reducing excess intake of calories, sugar, salt, and saturated fats. However, the importance of a positive message associated with promoting adequate nutrient intake as part of a balanced diet should not be overlooked. There is considerable variation in the consumption of food items that need to be encouraged and food items which should be limited, both between and within different countries. This was reflected in a recent study in European countries showing suboptimal nutrient-density of diets and significant proportions of the population consuming excess amounts of salt, sugar and saturated fat, as well as significant proportions of the population not meeting the required or adequate intakes for various essential nutrients, (Bruins, Dael & Eggersdorfer 2019; Greco et al., 2019).

Five most important mechanisms, which can mediate the pro-health and pro-longevity effects of the traditional Mediterranean diet, have been suggested to include: lipid-lowering effects, protection against oxidative stress, inflammation, and platelet aggregation, modification of hormones and growth factors involved in the pathogenesis of cancer, inhibition of nutrient-sensing pathways by specific amino acid restriction, and gut micro biota-mediated production of metabolites influencing metabolic health (Tosti, Bertozzi & Fontana, 2017).

What is already known?

The known truth is that diet is a modifiable risk factor that plays a role in the pathophysiology of non- communicable diseases.

What does this study add?

This study tends to argue the dimension and mechanism of dietary role in NCD pathophysiology and progression.

Objective

The purpose of this study is to elucidate the healthful and unhealthful diets and the mechanism by which diet is implicated in the pathophysiology of non-communicable diseases through a review of the evidence of debates from various studies.

Materials and methods

The review was conducted as a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Liberati et al., 2009). A literature search was conducted in Google Scholar, Medline, and PubMed for the relevant peer-reviewed studies published in the English language between 2016 and 2019 using the search terms diet, nutrients, Mediterranean diet, fruits, vegetables, dietary sugar, dietary fats, ketogenic diet, Non- communicable diseases,

cardiovascular disease, Cancer, Diabetes and Chronic Obstructive Pulmonary diseases.

Inclusion and exclusion criteria

Studies included in this review were those judged to be methodologically sound, high quality, objective, and reproducible; studies and reports previously conducted, peer-reviewed, and published between 2016 and 2019 relative to diet and health outcomes such as; cardiovascular diseases, cancer, chronic obstructive pulmonary disease, diabetes. The relevant studies were identified by screening the titles, abstracts, designs, texts, and papers. Findings associated with other modifiable behavioral risk factors like physical activity; alcohol consumption; smoking; and social activity other than diet or nutrition were excluded from the study.

The illustration flow chart for the study selection process is shown in figure 1 below. Studies excluded at the full paper screening stage are indicated along with the reason for exclusion and those that were finally included.

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow chart (Liberati et al., 2009) search results on the role of diet in the pathophysiology of non- communicable diseases.

Search results/ Findings

The searches for primary studies and the grey literature located 141 articles after removing duplicates, 124 of which had relevant titles and abstracts. In total, 41 studies that provide demonstrable focus on dietary habits or patterns and outcomes of the main non- communicable diseases; CVDs, COPDs, Diabetes, and Cancer informed the study review.

Diet and cardiovascular outcomes

Diet represents the most important modifiable factor to prevent cardiovascular diseases (CVDs) (Zhao, 2017), the evidence of beneficial aspects of plant-based dietary patterns to lower risk of CVDs have been proved with a positive impact (Lafortune, 2016). An accumulation of evidence presented by (Zhao, 2017) involving about 2,297,783 adults (men and women) aged between 20- 89 years from 11 countries confirmed a protective effect of various nutrients with an outcome range 0.53(95% CI: 28, 1.0)- 0.97(95% CI: 0.89, 1.01) such as polyphenols like anthocyanin, flavonoids, flavonols, flavones obtained from fruits including apples, pears, pomegranates, avocadoes, berries, hawthorns, oranges on cardiovascular conditions; Coronary heart disease (CHD), ischemic stroke, acute coronary syndrome(ACS), total stroke, hypertension and hemorrhagic stroke (Adriouch et al., 2018). However, further findings from cohort studies involving some 236, 685 adult men and women aged 49- 89 years from Italy, France, North Ireland, and Sweden failed to demonstrate an association between fruit intake and outcome of ACS, CHD and Ischemic heart disease (Tang et al., 2017). This evidence is strong due to the large number of studies involved though the findings are limited in the fact that the time frame for the studies is not elaborated.

Further still, a summary of evidence from numerous epidemiological studies indicates an inverse association between vegetables such as tomatoes, potatoes, onions, cereals, and cruciferous vegetables found to possess cardioprotective effects and CVD incidence. Moreover, a variety of bioactive components in vegetables have been proven to convey health benefits in preventing and treating CVDs, like botanical protein, dietary fiber, vitamins, essential elements, and phytochemicals. However, some studies found no significant inverse connection between vegetable consumption and CVD risks. On the one hand, researchers focused on the connection between vegetable flavonoid intake and CVD risk in women in a cohort study, only to find that for both CVDs and important cardiovascular events, there was no significant linear trend across quintiles of vegetable flavonoid consumption ($p = 0.63$ and 0.80, respectively), and neither for the individual flavonol or flavone. According to prospective data from another cohort study, broccoli consumption was not significantly associated with a reduction of CVD risk, and no significant association between broccoli flavonol or flavone consumption and nonfatal MI or fatal CHD risk was observed in U.S. women. The findings of another study indicated that habitually high consumption of soybean isoflavones might modestly but significantly increase the risks of ischemic stroke in women (Adriouch et al., 2018; Shannon et al., 2018).

Diet and diabetes

Diabetes is a serious, chronic disease that occurs either when the pancreas does not produce

enough insulin (a hormone that regulates blood glucose), or when the body cannot effectively use the insulin it produces. Raised blood glucose, a common effect of uncontrolled diabetes, may, over time, lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. More than 400 million people live with diabetes and are one of the biggest global public health problems: the prevalence is estimated to increase from 425 million people in 2017 to 629 million by 2045, with linked health, social, and economic costs (Farouhi et al., 2018).

Preventing and managing diabetes, particularly type 2 diabetes requires dietary modification particularly, a shift to plant-based foods such as legumes, seeds, nuts, whole grains, vegetables, fruits, and minimization of animal-based foods. A combination of an aging population plus sedentary life added to high-calorie foods such as; fast foods, meats, dairy products, highly refined grains, beverages sweetened with sugar are thought to play a critical role in the rising rates of type 2 diabetes worldwide (Hever & Cronise, 2017, Salas-Salvadó et al., 2019).

The mechanics of anti-diabetes action by plant-based diets are derived from the high fiber content, rich antioxidants, and elevated levels of magnesium, all of which are proven to be instrumental in the promotion of insulin sensitivity. Polyphenols with antioxidant properties inhibit the absorption of glucose, aid in the secretion of insulin, regulate the output of hepatic glucose, and enhance uptake of glucose. Fiber, a component that adds bulk to food and aids in digestion found only in plant foods, modulates postprandial glucose response, and is fermented by intestinal bacteria to produce short-chain fatty acids, which also improve the glucose response, insulin signaling and insulin sensitivity. Furthermore, fiber reduces the energy density of foods, promotes satiety, and has been associated with weight loss, which in turn reduces insulin resistance linked to decreased markers of inflammation (Moreno et al., 2017); Sami et al., 2017; Weickert & Pfeiffer, 2018).

In addition, diets high in saturated fat are associated with a predominantly gram-negative, lipopolysaccharide-rich gut microbial pattern, which also leads to insulin resistance and inflammation, the risk of developing type 2 diabetes, for example, increases by 20–40% for every 10 g of protein consumed more than 64 g/day (Tosti, Bertozzi & Fontana, 2017). A plant-based diet has also been shown to reduce visceral fat and improve markers of oxidative stress more than a conventional diet in individuals with type 2 diabetes. Advanced glycation end products are oxidant compounds high in meat (especially when grilled, broiled, roasted, seared, or fried), and low in plant-based foods such as fruits, vegetables, legumes, and whole grains (Frankenberg, 2017; Olfert & Wattick, 2018).

Iron from haeme (animal) sources is a pro-oxidant molecule that promotes insulin resistance through various likely mechanisms: increased oxidative stress leading to impaired insulin signaling, direct pancreatic beta-cell toxicity, decreased translocation of glucose transporter type 4 channels to the cell membrane, and increased hepatic glucose output. Other findings have found that in obese postmenopausal women, a low-calorie, high-protein diet prevented the therapeutic effect of weight loss on skeletal muscle insulin sensitivity likely due to worsening oxidative stress, as well as alterations in muscle cell structure and organization, induced by the high-protein diet (Mc Macken & Shah, 2017). It is also important to note that insulin resistance is exacerbated by obesity which in most cases is resultant of a prominent diet rich in refined grains and added sugars (Farouhi et al., 2018). The justification for a diet rich in whole-foods, plant-based foods that exclude animal products, refined grains, and added sugars will contribute to loss of excess weight and maintenance of healthier bodyweight and therefore encourage insulin sensitivity should raise no further debate. However, as noted previously, metabolic and epidemiological studies confirm that plant-based diets improve insulin sensitivity even when there is no weight loss, and/or with statistical adjustment for body weight (Frankenberg et al., 20017).

Diet and COPDs

Chronic obstructive pulmonary disease (COPD) is a progressive and irreversible airway disorder characterized by shortness of breath due to loss of elastic recoil of the lungs, leading to decreased total lung capacity and impaired gas exchange. It affects more than 5% of the population and is associated with high morbidity and mortality, COPD is the third most common cause of death in the United States and the fifth most common cause of death worldwide. Its

incidence and mortality rates are rising due to increasing worldwide non- adherence to a healthful diet comprising mainly fruits and vegetables. COPD pathophysiology involves chronic bronchitis and/or emphysema and sometimes chronic asthma (reversible airway hyperactivity). Chronic bronchitis is characterized by airway inflammation and defined by the presence of a productive cough and sputum production that lasts at least 3 months and occurs in more than 2 successive years. Emphysema entails abnormal and permanent enlargement of air spaces and destruction of the lung parenchyma, resulting in the closure of small airways and loss of lung elasticity (McMacken & Shah, 2017). Symptoms of COPD include dyspnea (distress with breathing), cough, and sputum production. Diagnosis, assessment, and management of COPD are mostly guided by the degree of airflow limitation as assessed by the forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and FEV1/FVC ratio, although other physiological measurements such as the inspiratory capacity to total lung capacity (TLC) ratio, arterial blood gases, and exercise capacity provide complementary information on the severity of the diseases (Bernard, 2018).

The pathogenic processes involved in COPD development and progression, include local and systemic oxidative stress (i.e. oxidants in excess compared with antioxidant capacity) and inflammation (neutrophils, macrophages, eosinophils, cytokines, chemokines, eicosanoids, Toll-like receptors, acute phase proteins), procatabolic status, protease/antiprotease imbalance, alteration of immune responses and cell proliferation, apoptosis, and cellular senescence, and remodeling of the small-airway compartment and loss of elastic recoil by emphysematous destruction of parenchyma (Liu & Chen, 2017). A further observation implicates oxidative stress in likely direct causation of lung damage through modification of DNA, lipids or proteins, as well as the initiation of cellular responses that can drive the inflammatory response within the lung, leading to lung tissue degradation (emphysema, fibrosis of small airways and remodeling of airway walls, ultimately impairing lung function (Siegel, Miller & Jemal, 2018).

Evidence compiled from a myriad of studies, after adjustment for multiple confounding factors known to influence pulmonary function or dietary behavior, including age, gender, body mass index (BMI), physical activity, intake of other foods or nutrients, energy intake, educational level, and most importantly, tobacco exposure, revealed that a diet comprising vegetables, fruits whole grains, polyunsaturated fatty acids, nuts, and long-chain omega-3 fatty acids and a low intake of red and processed meats, refined grains, and sugar-sweetened drinks increased lung function (FEV1, FVC, FEV1/FVC), symptoms, incidence, prevalence or severity of COPD, and its progression over time. Furthermore, the potentially protective effect of dietary factors is attributed to polyphenols, the most abundant antioxidants in human diets naturally present in plant foods that exhibit potent anti-inflammatory properties. Polyphenols include; phenolic acids, flavonoids (flavonols, flavones, isoflavones, flavanones, and anthocyanidins), stilbenes such as resveratrol, lignans, and secoiridoids (Bernard, 2018; Siegel, Miller & Jemal, 2018).

Diet and cancer

American Cancer Society defines cancer as a group of diseases characterized by the uncontrolled growth and spread of abnormal cells in which uncontrolled spread can result in death. Although the reason for the development of the disease remains unknown for many cancers, particularly those that occur during childhood, there are many known cancers causes, both modifiable and non-modifiable factors (Liu & Chen, 2017). The global cancer burden from 36 different cancer types is estimated to have risen to 18.1 million new cases and 9.6 million deaths in 2018. One in 5 men and one in 6 women worldwide develop cancer during their lifetime, and one in 8 men and one in 11 women die from the disease. Worldwide, the total number of people who are alive within 5 years of a cancer diagnosis, called the 5-year prevalence, is estimated to be 43.8 million (Siegel, Miller & Jemal, 2018).

The trend is increasing and by 2030, the global burden is expected to reach 21.6 million new cancer cases and 13.0 million cancer deaths solely due to the growth and aging of the population. These projections may increase given the adoption of unhealthy behaviors and lifestyles associated with rapid income growth including poor diet, among others such as physical

inactivity, tobacco use, and excessive alcohol intake (Bray et al., 2018).

Dietary factors are believed to account for 30%–35% of all cancers. Consumption of nutrients that contain elevated amounts of animal or caloric content, refined sugars, and alcohol increases cancer risk. In contrast, phytochemicals are thought to exert anticancer effects through various molecular pathways, such as free radical scavenging, modulation of hormonal and enzymatic activities, and induction of DNA damage in cancer cells (Ziaei & Halaby, 2018). A healthful life course approach to dieting is recommended to prevent a range of non-communicable diseases including cancer, for example; an adult should consume a healthy diet that contains vegetables, fruits, legumes, whole grains and nuts, less than 10% and 30% of total energy intake from free sugars and fats, respectively, as well as less than 5g of salt per day. Unsaturated fats are preferable to saturated fats and trans-fats should be reduced to less than 1% of total energy intake (Reboredo-Rodríguez, 2018).

Evidence from reviews of several studies revealed that carotenoids obtained from eating fruits and vegetables were linked to the development of various cancer sites such as Head and Neck cancers (HNC), Prostate (Pca), colon, Breast (Bca), cervical (Ca cervix). These carotenoids include; α- carotene. B- Carotene, γ-carotene, lycopene, retinol, lutein, β-cryptoxanthin, zeaxanthin, retinoids, Crocin, crocetin vitamin A, Curcumin, β-ionone, and α-ionone, astaxanthin and canthaxanthin. The carotenoids exhibit antioxidant activities such as quenching free radicals, reducing damage from reactive oxidant species, and inhibiting lipid peroxidation. Furthermore, carotenoids can play important roles in immuno-regulation and immunostimulation in vertebrates, anti-inflammatory, antimutagenic, anticarcinogenic roles by potently inhibiting cell proliferation, arrests of the cell cycle in different phases, and increasing apoptosis. The source for carotenoids includes; carrots, apricots, mangoes, red pepper, kale, spinach, broccoli, bananas, pumpkins, avocadoes, peas, cress, parsley, lettuce, maize, egg yolk, Tomato, Red watermelon, Pink grapefruit, Papaya, Guava, Rosehip canned (Milani et al ., 2017; Reboredo-Rodríguez et al 2018).

Findings from a large case-control study conducted in Italy between 1992 and 2009, aimed at establishing the effect of an inflammatory diet on the etiology of oral and pharyngeal cancer, suggested diet and inflammation be risk factors for oral and pharyngeal cancer. The study included 946 cases with the incident, histologically confirmed oral and pharyngeal cancer, and 2,492 controls hospitalized for acute non-neoplastic diseases. The findings portrayed a linear relationship between subjects who fed on a pro-inflammatory diet such as animal proteins, animal fat, saturated fatty acids, and cholesterol had a higher risk of oral and pharyngeal cancer, the OR being 1.80 (95% CI 1.36–2.38), compared to subjects who fed on an anti-inflammatory diet mainly; higher intakes of whole grains, fish, nuts, vegetables, fruit and plant-based components with an OR being 1.17 (95% CI 1.10–1.25) for a one-unit increase (8% of the dietary inflammation index) (Shivappa et al., 2017).

Conclusion

The role of diet in the pathophysiology of non-communicable diseases is complex, it is both a risk factor as well as protective. Whereas a diet high in carbohydrate, animal proteins, animal fats, saturated fats have proven to be oxidative, pro-inflammatory, pro- carcinogenic and pro-mutagenic, a diet composed of vegetables, fruits, legumes, fish, nuts, seafood, low fat, less of red meat (Mediterranean) have been proved to offer requisite health benefits and should be followed in a life-course manner. There are however major issues for the consideration of a healthful diet to prevent or treat various disorders including the efficiency of individual dietary nutrients which may depend on concentrations of other nutrients. Potential synergistic nutrient interaction and supplementation with a single nutrient may be ineffective; these compounds are highly sensitive to oxidation, chemical or enzymatic pathways, and consequently, they can be converted to other products, the effects of which are not fully known; different genetic susceptibility can lead to variations in the response to treatment with dietary nutrients among individuals with similar dietary intakes; and, the efficiency of dietary nutrients is determined in a time- and dose-dependent manner. However, the effect of individual dietary components, the time- dose-response, synergistic interactions of various dietary components, frequency, concentrations,

and quantities on non- communicable disease outcomes remain a subject for further study.

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